EXHIBIT "A"

In re: Application of TALTON, et al.

Application No.: 09/856,415 Examiner: SHEIKH, HUMERA.

Date Filed: July 2, 2001 Group: 1615

For: METHODS FOR PREPARING COATED DRUG PARTICLES AND PHARMACEUTICAL FORMULATIONS THEREOF

CERTIFICATE OF TRANSMISSION
I hereby certify that this correspondence is being transmitted to the Commissioner for Patents, Alexandria, VA, via facsimile to 703-872-9306.

Neil R. Jetter Reg. No. 46,803

RULE 132 DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, James D. Talton, Ph.D., declare as follows:

1. I am an inventor of the patent application No. 09/856,415 entitled "METHODS FOR PREPARING COATED DRUG PARTICLES AND PHARMACEUTICAL FORMULATIONS THEREOF" (hereafter the '415 application) and the subject matter described therein.

2. I hold a Ph.D. in Pharmaceutical Sciences (1999) and a M.S. (1995) in Materials Engineering from the University of Florida. Since 2000, I have worked regularly for 5 years as the CEO of a pharmaceutical drug delivery company, Nanotherapeutics, Inc., focusing on sustained-release systems and nanoparticles.

3. I have numerous nanoparticle-related publications that I have authored or co-authored including (3 of 7 total listed below):

i. A Novel Method for Polymer Coating of Plasmid DNA: Initial Investigations into the Use of Pulse Laser Deposition and Gene Delivery, H. Coulen, J. Hughes, J. Talton, G. Hochhaus, J Drug Targeting; Vol. 12 Issue 4, 237-41 (2004).

ii. Coating Powders for Drug Delivery Systems Using Pulsed Laser Deposition, J.D. Talton, B. Eppler, M.I. Davis, A.L. Mercado, J.M. Fitz-Gerald, In: D. Chrisey, Applications of Pulsed Laser Deposited Thin Films, Accepted (2004).

iii. Application of Matrix Assisted Pulsed Laser Evaporation Methods for the Development of Biodegradable Powder Coatings and Thin Films", A.L. Mercado, J. M. Fitz-Gerald, R. Johnson, C. Fraser, and J.D. Talton, Mat. Res. Soc. Proc., 780, pp. Y4.4.1, (2003).

4. I have reviewed the Final Office Action mailed December 3, 2004, and references cited therein, including U.S. Patent No. 5,223,244 to Moro et al. ("Moro"), U.S. Patent No. 5,976,577 to Green et al. ("'Green"), U.S. Patent No. 5,972,388 to Sakon et al., ("Sakon"), and U.S. Patent No. 5,855,913 to Hanes et al (Hanes).

5. The '415 application discloses an important new technology based on the use of a dry process referred to as pulsed laser ablation to coat core drug particles. As will be

described in some detail below, earlier conventional coating technologies, such as the references which rely on inherently wet spray-on processes which were cited by the Examiner, cannot provide the continuous nanoscale coatings on small (< 50 μm) core drug particles described and claimed in the '415 application.

The coating particles described in '415 are also biodegradable or biocompatible. The biodegradable or biocompatible coating layer provides controlled drug delivery, as evidenced by the dissolution profiles provided in the '415 specification.

6. The coated drug particles described in the '415 application includes particles which provide unexpected and/or new results by virtue of their size, including a change in function which permits new and highly advantageous applications. I do not dispute the Examiner's assertion that the "prior art recognizes limitations based on micron size particles", since it was known at the time of the invention that particles greater than about 20 to 50 μm in size are not inhalable by individuals. However, prior to the invention, continuously coated drug particles having sizes less than 50 μm in size were not obtainable.

Specifically, the size of Applicants' claimed nanoscale thick (1 to 500 nm) coated drug particles (< 50 μm in diameter) provide unique and unexpected biological responses. Particles according to the invention provide rapid and complete dispersion, as well as sustained release, such as for several hours. Sustained release is demonstrated through a release profile showing an essentially linear release rate over the period of several minutes to several hours (see Example 1, page 33, lines 18-20; Example 2 (beginning on page 34, line 28) demonstrating an improved sustained release rate profile compared to the uncoated drug particles. A 90% release occurred at approximately 12 hours (for coating at 2 hertz) and beyond 24 hours

(coating at 5 hertz), compared to uncoated drug particles that reached 90 % release at approximately 2 hours (see Figs. 6 and 7). Similarly, in Example 3 (page 36, lines 11-14), in vitro dissolution of coated rifampicin reached 90% release after 6 hours compared to 90% release after 15 minutes for the uncoated rifampicin (Fig. 8)).

Such sustained release profile obtained using continuously coated particles according to the invention were unexpected based on release data reported from somewhat thicker continuous coatings. The release profile for these thicker coatings are known to be characterized by a delayed release, rather than a sustained release, with no significant release throughout the first several hours. Sustained release for a drug is important in many applications. For example, regarding a painkiller, some early release (first few minutes) which is sustained for several hours keeps the concentration of the painkiller in the bloodstream above a therapeutic level for a long duration, such as 8-12 hours, rather than a burst release, whether with a delay or not, that is quickly (e.g. less than 1 hour of therapeutic use) carried away to the liver.

A hypothetical "micron-scale" continuously coated drug particle (>100 μm) is clearly too large to be used for inhalation (depositing in the mouth or throat) and release of the core drug over many hours to several days, and not generally obtainable by spray coating because the result from spray drying is inherently a continuous phase having a plurality of core particles therein, not the coated discrete drug particles which are claimed in the '415 Application.

7. Moro, Sakon and Hanes each teach spray drying to form coated particles. Spray drying is a process by which a plurality of species are generally first dissolved in a

solvent containing solution. In a typical process, one or more species may be insoluble in the solvent containing solution. Of these three (3) references, Only Moro discloses nanoscale coatings.

8. In Moro, a dry mixing process is used to form inert particles and potentially a drug in solution which are then spray dried onto a skin surface. The solution is sprayed onto a skin surface and then drying takes place.

9. In Sakon and Hanes, spray-drying occurs by spraying into an open chamber where the particles dry rapidly from a heated air-flow, generally from below, and the particles are suspended to aid drying.

10. In Moro, Sakon and Hanes, the solvent and other volatile species rapidly evaporate to leave a random mixture of the remaining non-volatile species intermixed, with the resulting layer formed having significant porosity from the solvent evaporation process. No distinguishable coating layer is formed on any species since the arrangement of particles following drying is random, being a porous continuous phase having a plurality of core particles therein. As a result, spray drying does not form a plurality of coated particles, and clearly cannot provide a medicament comprising < 50 micron core drug particles coated with a nanoscale continuous and non-porous coating layer.

11. Green is used by the Examiner in combination with Moro, Sakon and Hanes in an attempt to overcome the deficiencies of Moro, Sakon and Hanes

acknowledged by the Examiner regarding spray-dry derived coatings which are non-continuous and non-porous when disposed on small (< 50 micron core particles). As explained below, Green cannot cure the deficiencies of Moro, Sakon and Hanes acknowledged by the Examiner because Green is not combinable with Moro, Sakon or Hanes.

12. Green discloses a process for preparing an oral solid rapidly disintegrating freeze-dried bulk dosage form (tablet) which includes a plurality of drug particles which if tasted would have an unacceptable taste. Green relies on "current coating techniques", such as to provide drug particles (e.g. paracetamol 200 μm) coated with a water insoluble polymer and notes that "Current coating techniques are able to effectively coat particles greater than 100 μm, whereas particles less than *100 μm may not have an intact coat*, which will result in rapid release of the drug once in suspension." (col. 3, lines 9-21). Therefore, although Green's teaching of particles generally having an average size up to 500 μm would mathematically include particle sizes less than 100 μm as asserted by the Examiner, particles having sizes less than 100 μm are not included by Green because they lack "an intact (continuous) coat".

Prior to freeze drying, a suspension of the coated (or uncoated) drug particles are disposed in a carrier material (e.g. water and dissolved gelatin) which is then cooled to reduce the viscosity and minimize release rate of the active substance during processing, as well as beyond the point of disintegration of the form in the mouth, to minimize bad taste from the drug. The continuous phase (e.g. water) portion of the carrier material is removed to result in a final composition which is generally 1 mm or greater in size discrete units containing up to 250 mg of the drug (col. 6 line 49), such as tablet shaped articles with small (uncoated or

coated) drug particles dispersed throughout. The resulting tablet thus includes a plurality of drug particles in continuous phase of freeze dried coating material (such as gelatin), not discretely coated drug particles.

13. The intermediate coated drug particles formed by the non-ascertainable "current coating techniques" are disclosed by Green as having to be at least 100 μm, or more (e.g. 500 μm) in size to permit the formation of a continuous coating thereon. Green's "current coating technique" relied on is likely the spray drying technique disclosed by Moro, Sakon and Hayes, but cannot be sure because of the absence of any specifics. Accordingly, the "current coating techniques" alluded to by Green provides no teaching that can be used to improve upon the spray dry coating results obtainable using the processes disclosed by Moro, Sakon or Hayes. Therefore, Green's intermediate coated particles and associated method are not combinable with the coated particles and associated spray-on method disclosed by Moro, Sakon or Hayes. As a result, the compositions provided by Moro, Sakon or Hayes cannot benefit from a knowledge of Green to achieve "a continuously coated, non-porous pharmaceutical formulation that exhibits a sustained release of the active drug material" as asserted by the Examiner.

14. Moreover, although apparently overlooked by the Examiner in the Office Action, the spray-on process disclosed by Moro, Sakon or Hayes inherently results in *a porous continuous phase having a plurality of core particles therein*. Green's teaching, or more correctly lack of teaching thereof regarding coating of particles, cannot overcome this deficiency inherent to spray coating processes.

15. Green's teaching relates to placing coated drug particles suspension process to form a bulk dosage form (fast-dissolving tablet) incorporating a plurality of drug particles. This teaching would clearly be of no benefit to Moro, Sakon or Hayes.

16. It is my opinion that spray drying cannot form a plurality of coated particles as it instead forms *a porous continuous phase having a plurality of core particles therein. Moreover, spray drying* clearly cannot provide a medicament comprising < 50 micron core drug particles coated with a nanoscale continuous and non-porous coating layer. Applicants' claim 28 which recites a plurality of coated drug particle having a diameter of less than 50 μm, the coating layer being a continuous and non-porous layer, having an average thickness of the between 1 and 500 nm is thus not obtainable in my opinion based on the cited art, whether alone or in combination.

17. I further state that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dr. James Talton

3/2/05
Date